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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Ex parte RICHARD C. KLANN, FRANCIS V. LAMBERTI, and RONALD S. HILL[1]

Appeal 2015-007751
Application 12/274,765
Technology Center 1600

Before ULRIKE W. JENKS, RICHARD J. SMITH, and DEVON ZASTROW NEWMAN, *Administrative Patent Judges*.

NEWMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This decision on appeal under 35 U.S.C. § 134 involves claims to methods of cryopreservation using hydrogels. The Examiner entered final rejections for obviousness.

We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

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[1] Appellants identify the Real Party in Interest as RTI SURGICAL, INC. Br. 1.

STATEMENT OF THE CASE

Background

The Specification teaches cryopreservation using a hydrogel matrix, explaining that the hydrogel matrix:

> provides a scaffold for cell attachment before, during, and after cryopreservation and that can be directly used *in vitro* or *in vivo* to deliver the previously cryopreserved cells to a site of interest or need. The bioactive hydrogel matrix can thus function as a growth substrate for cells, as a carrier for long-term storage during cryopreservation, and as a delivery device after resuscitation of cryopreserved cells. Moreover, the bioactive hydrogel matrix can actually provide therapeutic benefits in association with the cell delivery, including modulation of localized wound healing and tissue integration. The cells may be at least partially retained on an exposed surface on the hydrogel matrix particles. In further embodiments, the cells may be at least partially retained within one or more pores present in the hydrogel matrix particles.
>
> . . .
>
> The hydrogel may be comprised completely of natural components, may be comprised completely of synthetic components, or may comprise a combination of natural and synthetic components. Examples of natural components include, but are not limited to, naturally occurring proteins and polypeptides and naturally occurring polyglycans, such as polysaccharides. Specific examples of synthetic hydrogels that may be used according to the invention include hydrogels comprising polyethylene glycol (PEG), acrylates, methacrylates (e.g., 2-hydroxyethyl methacrylate or pHEMA), and polyvinyl alcohol.

Spec. 3.

The Claims

Claims 1–6, 8–19, 21–25, 27–30, 32–41, 43, and 44 are on appeal.[2]

Independent claims 1, 30, and 44 are illustrative and read as follows:

1. A method of cryopreserving cells comprising subjecting particles of a cross-linked bioactive hydrogel matrix to cryopreservation conditions, wherein said hydrogel matrix particles and the cells for cryopreservation are combined such that the cells are attached to an exposed surface of the hydrogel matrix particles when the combination of the cells and the particles is subjected to the cryopreservation conditions.

30. A cell-seeded composition comprising the combination of particles of a cross-linked bioactive hydrogel matrix and cells, the cells being attached to the hydrogel matrix particles, the composition being in a cryopreserved form.

44. A cell-seeded composition comprising particles of a crosslinked bioactive hydrogel matrix, cells that are attached to the hydrogel matrix particles, and a cryoprotectant.

Br. (Claims App'x.) 23, 27, and 30.

The Issues

The following rejections are before us to review (Ans. 2):

Claims 1, 2, 8–13, 17–19, 21–25, 27, 28, 30, 32–35, and 37–41 are rejected under 35 U.S.C. § 103(a) as obvious over Frondoza.[3]

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[2] Although Appellants state "all of claims 1–6, 8–30, and 32–44 are appealed herein," claims 20, 26, and 42 are withdrawn and are therefore not addressed herein. Br. 2.

[3] U.S. Publication No. 2004/0117033 A1, published June 17, 2004, to Frondoza et al. (hereinafter "Frondoza").

Claims 14–16 and 36 are rejected under 35 U.S.C. § 103(a) as obvious over Frondoza and Qian.[4]

Claim 29 is rejected under 35 U.S.C. § 103(a) as obvious over Frondoza and Hill.[5]

Claims 3–6, 43, and 44 are rejected under 35 U.S.C. § 103(a) as obvious over Frondoza and Usala.[6]

The Examiner finds that Frondoza teaches "a microcarrier cell culture method that facilitated maintenance of a specific phenotype while enhancing proliferation, where cells (e.g., articular chondrocytes) were grown on dextran or crosslinked collagen microcarrier beads under controlled pH, oxygen levels, nutrient supply[,] and mechanical agitation conditions" and "a method of culturing cells within this microcarrier system." Ans. 5. The Examiner finds that Frondoza teaches "cells that are attached to a surface of the microcarrier beads may be cryopreserved by standard methods in order to maintain cell viability." *Id.* at 6.

The Examiner finds that although Frondoza teaches "the microcarrier particle can be a cross-linked collagen or can comprise of organic materials such as gelatin, dextran, hydrogels, etc. . . . Frondoza does not explicitly indicate that the microcarrier particle is a cross-linked gelatin-dextran hydrogel." *Id.* at 7. The Examiner finds that because "Frondoza indicates

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[4] U.S. Publication No. 2007/0248685 A1, published Oct. 25, 2007, to Qian et al. (hereinafter "Qian").
[5] U.S. Publication No. 2005/0118230 A1, published June 2, 2005, to Hill et al. (hereinafter "Hill").
[6] U.S. Patent No. 6,730,315 B2, issued May 4, 2004, to Usala et al. (hereinafter "Usala").

that the microcarrier may be organic resorbable materials which might include biopolymers (e.g. collagen, gelatin, dextran, etc.) or chemically modified derivatives of these materials (e.g., cross-linked derivatives) as well as hydrogels or any other synthetic polymers that can be produced in appropriate bead form", the combination of two compositions disclosed in Frondoza for the specific purposes would be obvious. *Id.* at 7.

The Examiner concludes that, based on the teachings of Frondoza, it would have been obvious "to combine organic resorbable materials (such as dextran and gelatin) to produce a crosslinked hydrogel in appropriate bead (i.e., particle) form, since each organic material is taught to be useful as a microcarrier particle used for cell attachment, and that once attached, the cell-microcarrier particle can be cryopreserved." *Id.* at 8. The Examiner concludes that because Frondoza discloses

> all of the limitations . . . expressly suggested as suitable for inclusion within Frondoza's microcarrier particles . . . a person of ordinary skill at the time the invention was made would have been motivated to combine the recited components as described above (i.e., crosslinked gelatin-dextran hydrogel microcarrier, cells that are attached on an exposed surface of the microcarrier particle, and then the combined particle-cell is cryopreserved under standard methods), with a reasonable expectation of success since Frondoza teaches that these are desirable components within its cell-based composite.

Id.

The Examiner finds the claims obvious because Frondoza teaches "a cross-linked hydrogel matrix [which is] the final product," that "the starting material can be cross-linked collagen, and that other starting materials such

as collagen, gelatin, or chemically derived modifications of dextran, agarose, or calcium alginate can be used." *Id.* at 21.

The Examiner relies on Usala to teach "cryoprotectant (e.g., sulfated dextran) may be added that allows a matrix to be stored at lower temperatures without cellular damage." Ans. 13. The Examiner concludes that it would have been obvious to a person of ordinary skill in the art "to combine Frondoza and Usala since cryopreservation temperatures in standard cryopreservation methods are routinely used and are well known in the art, and the addition of a cryoprotectant allows a matrix to be stored at lower temperatures without cellular damage" and that the combination would have had "a reasonable expectation of success . . . since both are involved in tissue engineering and cell preservation." *Id.* at 14.

The Examiner relies on Qian to teach "a cross-linked gelatin dextran hydrogel powder having a particle size in the range from 150 μm to 750 μm; Qian also teaches that particle sizes outside of this range may find use in many circumstances." *Id.* In light of these teachings, the Examiner finds it would have been obvious "to grind (mill) the cross-linked bioactive hydrogel matrix to a particular particle size range." *Id.* at 11.

The Examiner relies on Hill to teach dehydration of a hydrogel matrix, including by lyophilization. Ans. 11. The Examiner concluded it would have been "obvious . . . to dry and mill the cross-linked bioactive hydrogel matrix based on the teachings in Hill so as to provide a cross-linked bioactive hydrogel matrix that is easy to store, preserves the shelf life of the material, as well as provides a customized particle size." *Id.* at 12.

The issue with respect to these rejections is whether a preponderance of the evidence of record supports the Examiner's conclusion that the claims are obvious over the cited art.

Findings of Fact

1. The Specification teaches "a stabilized cross-linked bioactive hydrogel matrix that provides a scaffold for cell attachment before, during, and after cryopreservation and that can be directly used *in vitro* or *in vivo* to deliver the previously cryopreserved cells to a site of interest or need." Spec. 3:4–7.

2. The Specification teaches

> [t]he hydrogel may be comprised completely of natural components, may be comprised completely of synthetic components, or may comprise a combination of natural and synthetic components. Examples of natural components include, but are not limited to, naturally occurring proteins and polypeptides and naturally occurring polyglycans, such as polysaccharides. Specific examples of synthetic hydrogels that may be used according to the invention include hydrogels comprising polyethylene glycol (PEG), acrylates, methacrylates (e.g., 2-hydroxyethyl methacrylate or pHEMA), and polyvinyl alcohol.

Spec. 3:16–23.

3. The Specification teaches:

> In certain embodiments, the hydrogel matrices of the invention may comprise a first high molecular weight component and a second high molecular weight component covalently cross-linked to the first high molecular weight component. The first high molecular weight component and the second high molecular weight component particularly can be selected from the group consisting of

> polyglycans and polypeptides. The polyglycan can particularly be a polysaccharide or a derivatized polysaccharide (e.g., sulfates, acetates, phosphates, and ammonium salts of polysaccharides) and can include polysaccharides such as commonly found in biofilms or extracellular matrices. The polyglycans, for example, and can be selected from the group consisting of dextran, heparan, heparin, hyaluronic acid, alginate, agarose, carageenan, amylopectin, amylose, glycogen, starch, cellulose, chitin, chitosan, heparan sulfate, chondroitin sulfate, dextran sulfate, dermatan sulfate, and keratan sulfate. The polypeptide can be selected from the group consisting of collagens, gelatins, keratin, decorin, aggrecan, glycoproteins, laminin, nidogen, fibulin, and fibrillin. In one embodiment, the polyglycan can be dextran and the polypeptide can be gelatin.

Spec. 3:24–4:7.

4. The Specification teaches "[t]he bioactive hydrogel matrix can be in particulate form when combined with the cells for cryopreservation." Spec. 4:15–16.

5. Frondoza teaches:

> a microcarrier spinner culture system that facilitated maintenance of chondrocytic phenotype while enhancing proliferation. Articular chondrocytes were grown on dextran or crosslinked collagen microcarrier beads under controlled pH, oxygen levels, nutrient supply and mechanical agitation conditions. This represents a great advantage over the traditional static monolayer culture system, which facilitates proliferation but leads to a fibroblastic shift in phenotype. Likewise, it offers an alternative to the battery of three-dimensional gel or scaffold systems, which include agarose or collagen gels,

> calcium alginate gel, mixed fibrin-alginate gels, three-dimensional meshes of resorbable polymers such as polylactides or polyglycolides, and encapsulation in alginate beads. These latter culture techniques facilitate the maintenance of a chondrocytic phenotype, but are limited in maximizing proliferation.

Frondoza ¶ 3.

6. Frondoza teaches:

> a method of preparing cells for implantation comprising allowing cells (e.g., chondrocytes) to grow on microcarrier particles for an extended period of time and to secrete extracellular matrix components, thereby producing a cell-microcarrier aggregate useful for transplantation to a patient. The cell-microcarrier aggregates can be implanted directly or further cultured inside a mold that has been shaped to configure the geometry of the area of the body receiving the cells for transplantation. When further cultured in a mold, cell microcarrier aggregates are consolidated into an implantable structure for repair or replacement of missing or diseased tissue. The microcarrier used to prepare the aggregate is a biocompatible, biodegradable material. This method also anticipates that cell-microcarrier aggregates, or consolidated implants prepared therefrom by further culturing in a mold, may be cryopreserved by standard methods in order to maintain cell viability and aggregate structure for future implantation or analysis.

Frondoza ¶ 4.

7. Frondoza teaches "the implantation of a combination of (1) cell-microcarrier aggregates or cell-scaffold or cell-free biomaterial

formulations in a solid implantable format; and (2) cells or cell-microcarrier aggregates in an injectable format. Frondoza ¶ 15.

8. Frondoza teaches:

> The microcarrier may be inorganic or organic resorbable materials suitable for maintaining seeded cells in culture. Inorganic materials include, for example: calcium phosphates, calcium carbonates, calcium sulfates or combinations of these materials. Organic materials might include, for example: biopolymers such as collagen, gelatin, hyaluronic acid or chemically derived modifications of hyaluronic acid, chitin, chitosan or chitosan derivatives, fibrin, dextran, agarose, or calcium alginate, particles of tissue such as bone or demineralized bone, cartilage, tendon, ligament, fascia, intestinal mucosa or other connective tissues, or chemically modified derivatives of these materials. Organic materials might also include synthetic polymeric materials, including, for example: polylactic acid, polyglycolic acid or copolymers or combinations of the two, polyurethanes, polycarbonates, poly-caprolactones, hydrogels such as polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines, or any other synthetic polymers that can be produced in appropriate bead form.

Frondoza ¶ 17.

9. Frondoza teaches:

> a material capable of polymerizing or gelling after implantation may be mixed with the aggregate suspension prior to implantation in order to improve the fixation and localization of the aggregates after implantation, to stimulate more rapid consolidation of the aggregates in vivo, or to promote more rapid integration of the aggregates into the surrounding tissue. Examples of such binding materials are .

> . . collagen, combinations of fibrin glues and collagen, transglutaminase-catalyzed binding systems, hydrogels such as polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines, or similar materials with suitable gelling compositions. In situ gelling of these materials may be initiated by thermal, enzymatic or chemical catalysts, pH or ionic strength changes or photo-initiation procedures.

Frondoza ¶ 18.

10. Frondoza teaches that a "solid formulation may [be] formed by the extended culturing of chondrocytes or stem cells, for example, on porous, biocompatible solid scaffolds suitable for implantation into the body." Frondoza ¶ 33.

11. Frondoza teaches that a composition "for producing an injectable cell-microcarrier aggregate suspension containing a gel-forming system" can include "collagen, combinations of fibrin/collagen, transglutaminase-catalyzed binding systems, hyaluronic acid, calcium alginate gels, chitosan derivatives capable of gelling at body temperature, hydrogels such as polyacrylates, polyvinyl alcohols, polyethylene glycols, or polyethyleneimines, or similar materials with suitable gelling compositions." Frondoza teaches that "[i]n situ gelling of these materials may be initiated by thermal, enzymatic or chemical catalysts, pH or ionic strength changes or photo-initiation procedures." Frondoza ¶ 37.

12. Frondoza teaches a "solid implant [that] is made by culturing cells on a porous biodegradable scaffold." Frondoza 6, claim 13.

13. Usala discloses "[a] method of maintaining cell viability and functioning during storage is provided wherein the cells are imbedded in the hydrogel matrix of the present invention." The matrix protects cells during

storage, including frozen storage, which is disclosed as "at least -20º C." Usala 2:62–65; 11:40–43.

14. Usala teaches a hydrogel matrix for long-term storage and proliferation of cellular tissue. One hydrogel matrix composition is a mixture of:

> gelatin;
> dextran or sulfated dextran;
> at least one polar amino acid; and
> about 1 to about 8 mM of a divalent chelator, the divalent chelator comprising EDTA.

Another hydrogel matrix composition is a mixture of:

> denatured collagen;
> dextran or sulfated dextran;
> an L-arginine analogue; and
> at least one polar amino acid selected from the group consisting of arginine, lysine, histidine, glutamic acid, aspartic acid, and mixtures thereof.

Usala 18:1–16, claims 23 and 24.

15. Usala discloses:

> For long term storage, an effective amount of cryoprotectant may be added that allows the matrix to be stored at lower temperatures without cellular damage. Preferably, the cryoprotectant is metabolically stable and capable of creating an inert cushion to prevent thermal expansion and contraction of cells. A preferred cryoprotectant is sulfated dextran.

Usala 11:53–55.

16. Qian teaches "[t]he compositions comprise a dry cross-linked gelatin powder which has been prepared to re-hydrate rapidly . . . A preferred particle size [of gelatin] will be the range from 150 μm

to 750 μm, but particle sizes outside of this preferred range may find use in many circumstances." Qian ¶ 10.

17. Qian teaches:

> After cross-linking, at least 50% (w/w) of the re-hydration aid will be removed from the resulting hydrogel. Usually, the re-hydration aid is removed by filtration of the hydro gel followed by washing of the resulting filter cake
> . . .
> After filtration, the gelatin is dried, typically by drying the final filter cake which was produced. The dried filter cake may then be broken up or ground to produce the cross-linked powder having a particle size in the desired ranges set forth above.

Qian ¶¶ 17–18.

18. Qian teaches that the cross-linked "powder has a mean particle size in the range from 150 μm to 750 μm." Qian 7:3–4, claim 41.

19. Hill teaches:

> In addition to being in its usual, hydrated form . . . the bioactive hydro gel matrix . . . can further be in a dehydrated form . . . Any method generally known in the art for dehydrating materials normally in a hydrated state would be useful according to the present invention, so long as it is not detrimental to the connective tissue regenerative properties of the hydrogel matrix as described herein. For example, one preferred method of dehydrating the bioactive hydrogel matrix is freeze drying.
> . . .
> Freeze drying generally comprises the removal of water or other solvent from a frozen product through sublimation, which is the direct transition of a material (e.g., water) from a solid state to a gaseous state without passing through the liquid

> phase. Freeze drying allows for the preparation of a stable product being readily re-hydratable, easy to use, and aesthetic in appearance. The freeze drying process consists of three stages: 1) pre-freezing, 2) primary drying, and 3) secondary drying.
>
> Hill ¶¶ 87–88.

20. Hill teaches "[t]he dehydrated hydrogel matrix could also be ground to a particulate form." ¶ 94.

Principles of Law

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex Inc.,* 550 U.S. 398, 416 (2007). "If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." *Id.* at 417.

Wrigley found a "strong case of obviousness based on the prior art references of record. [The claim] recites a combination of elements that were all known in the prior art, and all that was required to obtain that combination was to substitute one well-known . . . agent for another." *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC,* 683 F.3d 1356, 1364 (Fed. Cir. 2012).

DISCUSSION

The Examiner provides sound based reasoning for rejecting claims 1, 2, 8–13, 17–19, 21–25, 27, 28, 30, 32–35, and 37–41 as obvious over Frondoza, Usala, Qian, and Hill. We adopt and incorporate by reference the Examiner's findings and conclusions as presented in the Final Action mailed

August 8, 2014, and Answer. We adopt the fact finding and analysis of the Examiner as our own as Findings of Fact 1–20. As noted by the Examiner, Appellants responded to all rejections "as a compilation of arguments based on the rejection under 35 U.S.C. § 102(a) to Frondoza." Ans. 16. We address Appellants' arguments in a similar manner below, with analysis directed to the secondary references addressed by Appellants within Appellants' combined arguments.

We begin with claim interpretation because it is at the heart of patent examination as a claim cannot be compared to the prior art before its scope is properly ascertained. *Cf. In re Abbott Diabetes Care Inc.,* 696 F.3d 1142, 1146 (Fed. Cir. 2012)). "[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000). We first turn to the Specification to interpret the term "cross-linked bioactive hydrogel matrix."

The Specification provides: "a stabilized cross-linked bioactive hydrogel matrix that provides a scaffold for cell attachment before, during, and after cryopreservation and that can be directly used *in vitro* or *in vivo* to deliver the previously cryopreserved cells to a site of interest or need." Spec. 3:4–7. The Specification provides various suitable components for cross-linked bioactive hydrogel matrices and states "[t]he bioactive hydrogel matrix can be in particulate form when combined with the cells for cryopreservation." FF1–3. We agree with the Examiner that the Specification does not provide a definition for "cross-linked bioactive hydrogel matrix" and merely describes suitable components and

embodiments. Ans. 4. The requirement that the hydrogel provide a scaffold for cell attachment before, during, and after cryopreservation and that it can be directly used *in vitro* or *in vivo* to deliver the previously cryopreserved cells also does not impart further structural limitations. FF1. The broadest reasonable interpretation of "cross-linked bioactive hydrogel matrix" in light of the Specification is a generic cross-linked bioactive hydrogel matrix. Ans. 4.

Turning to Appellants' arguments, the Appellants contend that the Examiner's finding that "Frondoza teaches that crosslinked collagen microcarrier beads equate to a cross-linked hydrogel matrix particle as presently claimed" is incorrect because "a person of skill in the art would not view Frondoza as teaching a *cross-linked hydrogel matrix particle.*" Appellants argue

> "[a] person of ordinary skill in the art would recognize crosslinked collagen beads as being a very specific material that is formed by highly crosslinking collagen upon itself, typically with glutaraldehyde crosslinking. Crosslinked collagen beads are not particles of a hydrogel matrix and a person of skill in the art would not only recognize the difference but would recognize that paragraph [0003] of Frondoza expressly distinguishes between the materials.

Br. 8–9. Further, Appellants argue Frondoza "teaches that crosslinked collagen beads 'offer[] an alternative to the battery of three-dimensional gel or scaffold systems, which include agarose or collagen gels,'" which is necessary because, as Frondoza discloses, "three-dimensional gel or scaffold systems do not provide desired cell proliferation." Appellants argue the skilled artisan would "recognize that Frondoza teaches away from three-

dimensional gel or scaffold systems, and such person would limit any extension of Frondoza to beads and not hydrogels" and "would not seek to prepare such a hydro gel and use it in a cryopreservation method." *Id.* at 9–10. These arguments are not persuasive.

Frondoza teaches a method of culturing cells within a microcarrier system, by growing cells on dextran or cross-linked collagen microcarrier beads (i.e., a cross-linked hydrogel matrix particle) under controlled conditions. FF5–12. Frondoza teaches allowing cells to grow on microcarrier particles in which the microcarrier used to prepare the aggregate is a porous biocompatible, biodegradable material and that the cells that are attached to a surface of the microcarrier beads may be cryopreserved by standard methods in order to maintain cell viability. FF8.

While Frondoza recognizes that use of "three-dimensional gel or scaffold systems" may limit maximizing cell proliferation, Frondoza discloses and claims scaffolding systems as embodiments of the invention. Frondoza states "[c]ontemplated in this invention is the implantation of a combination of (1) cell-microcarrier aggregates or cell-scaffold or cell-free biomaterial formulations in a solid implantable format; and (2) cells or cell-microcarrier aggregates in an injectable format." FF7. Further, Frondoza specifies that hydrogels may be used for "polymerizing or gelling after implantation may be mixed with the aggregate suspension prior to implantation in order to improve the fixation and localization of the aggregates after implantation." FF9.

"Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to

produce the objective of the applicant's invention. A statement that a particular combination is not a preferred embodiment does not teach away absent clear discouragement of that combination." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005) (citations omitted). Because Frondoza encourages rather than discourages scaffolding systems, Frondoza does not teach away from their use.

Appellants offer no support for their statement that "[c]rosslinked collagen beads are not particles of a hydrogel matrix." Br. 9. The Specification states that hydrogel matrix embodiments "may include a first high molecular weight component and a second high molecular weight component covalently cross-linked to the first high molecular weight component" and that those components "can be selected from the group consisting of polyglycans and polypeptides." FF3. Dextran is listed as an example polyglycan and collagen as an example polypeptide. *Id.* The Specification further states "[t]he bioactive cross-linked hydrogel matrix utilized in each of the embodiments described herein may be comprised solely of the two high molecular weight components cross-linked to one another." 27:11–13. The Specification does not define "components." Therefore, the dextran and cross-linked collagen microcarrier beads disclosed by Frondoza (FF5) fall within the Specification's disclosed embodiments for a generic cross-linked bioactive hydrogel matrix.

Appellants next argue that "[n]othing in Frondoza discloses or suggests that a 'chemically modified derivative' means crosslinked" and that because Frondoza "suggests a 'chemically modified derivative' of bone, demineralized bone, cartilage, tendon, ligament, fascia, or intestinal mucosa,

one of skill in the art clearly would not interpret this phrase to mean crosslinking." Br. 10. These arguments are not persuasive.

Frondoza discloses that a material capable of polymerizing or gelling may be used to stimulate rapid integration of aggregates into surrounding tissue and lists examples of binding materials. FF9, 11. Frondoza teaches these materials may be gelled in situ by thermal, enzymatic or chemical catalysts, pH or ionic strength changes or photo-initiation procedures. FF11. We agree with the Examiner that "[s]uch materials and techniques (e.g., enzymatic, chemical catalysts, photo-initiation procedures) are well known techniques that involve crosslinking and chemical crosslinking in the tissue engineering arts." Ans. 22; see also Qian ¶ 10. Moreover, Frondoza discloses growth of articular chondrocyte cells on crosslinked collagen microcarrier beads. FF5.

Appellants next argue

> The examiner has not pointed to any teaching in Frondoza that would lead a person of skill in the art to take any of the materials disclosed therein, form a hydro gel, cross-link the hydrogel, particularize the hydrogel, attach cells to the particles of the cross-linked hydro gel, and subject the combination of cells and particles to cryopreservation conditions. Such level of teaching is necessary for a person of skill in the art to make the leap from Frondoza to the presently claimed subject matter.

Br. 11. Similarly, Appellants argue "[a]though . . . Frondoza teaches that the prior art cell-microcarrier aggregates may be cryopreserved, Frondoza still does not teach particles of a cross-linked hydro gel matrix that have [c]ells attached thereto and that is in a cryopreserved condition." *Id.* Appellants also argue "Frondoza does not teach forming a hydrogel, cross-linking a

hydrogel, and particularizing the cross-linked hydrogel." Br. 13. Appellants also argue "the presently recited particles of a cross-linked hydrogel matrix are nowhere suggested by Frondoza because the document does not teach that particles of hydrogels may be used as a cell attachment scaffold for cryopreservation of cells." Br. 14–15. According to Appellants, "the present claims do not recite the combination of two compositions that are each expressly taught to be useful for the same purpose." *Id.* at 15. Appellants further argue "nothing in Frondoza suggests cross-linking together two specific materials, particularly a polyglycan and a polypeptide." Br. 19.

These arguments are not persuasive because the Examiner's rejection is based on obviousness, not anticipation. Further,

> [a] claim can be obvious even where all of the claimed features are not found in specific prior art references, where 'there is a showing of a suggestion or motivation to modify the teachings of [the prior art] to the claimed invention.' *SIBIA Neurosciences, Inc.* v. *Cadus Pharm. Corp.,* 225 F.3d 1349, 1356 (Fed. Cir. 2000) (concluding that patent would have been obvious in light of teachings in prior art which provided motivation and suggestion to modify existing techniques to arrive at method in question).

Ormco Corp. v. *Align Technology Inc.,* 463 F.3d 1299, 1307 (Fed. Cir. 2006). Moreover, "interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all [can provide] an apparent reason to combine the known elements in the fashion claimed." *KSR Int'l Co.* v. *Teleflex Inc.,* 550 U.S. 398, 418 (2007).

Here, the Examiner has combined the components disclosed in Frondoza as the skilled artisan would have been motivated to do so based on the teachings in the reference to show that each element of claims 1, 2, 8–13, 17–19, 21–25, 27, 28, 30, 32–35, and 37–41 would have been obvious or inherent based on the physical and chemical properties of the components and the ways in which Frondoza has taught they may be used and combined. Appellants have presented insufficient persuasive evidence, and provided only attorney argument, that the skilled artisan would not have been so motivated to create the combination. As discussed above with respect to "components," Frondoza teaches components used in the same manner as those claimed by Appellants.

With regard to Appellants' contention that "the examiner has not shown that a person of ordinary skill in the art, without knowledge of the present claims, could select specific components from Frondoza, make modifications thereto, and arrive at the [claimed] methods and compositions," (Br. 8), we note that our reviewing court has stated that "picking and choosing may be entirely proper in the making of a 103, obviousness rejection. . . but it has no place in the making of a 102, anticipation rejection." *In re Arkley*, 455 F.2d 586, 587 (CCPA 1972) (emphasis removed). The instant rejection is for obviousness. Both Frondoza and the Specification disclose various components for the purpose of creating cell-binding systems (e.g., microcarriers such as hydrogels) that may be cryopreserved. See e.g., FF 2, 3, 5, 8 and 9. We agree with the Examiner that the skilled artisan would find it obvious to combine the disclosed components as claimed.

Appellants next argue the Examiner has failed to "point[] to any portion of Frondoza providing predictability in relation to using particles of a cross-linked hydrogel matrix as an attachment scaffold for cells and cryopreserving such combination of the cells and the particles of a cross-linked hydro gel matrix." This argument is not persuasive. "Obviousness does not require absolute predictability of success. . . . For obviousness under § 103, all that is required is a reasonable expectation of success." *In re O'Farrell*, 853 F.2d 894, 903–04 (Fed. Cir. 1988). Appellants have presented insufficient persuasive evidence, and provide only attorney argument, that the skilled artisan would not be successful in using particles of a cross-linked hydrogel matrix as an attachment scaffold for cells and cryopreserving the matrix as disclosed by Frondoza. Appellants' arguments without more do not meet this requirement. *See In re Geisler*, 116 F.3d 1465, 1470 (Fed. Cir. 1997) ("[A]ttorney argument [is] not the kind of factual evidence that is required to rebut a prima facie case of obviousness").

Appellants argue claims 43 and 44 are not obvious because Frondoza does not "suggest[] a cell-seeded composition wherein particles of a cross-linked hydrogel matrix with cells attached thereto are in combination with a cryoprotectant" and because a skilled artisan "viewing Frondoza would not predict that such combination is useful or even possible." Br. 11. Appellants argue the skilled artisan would read Usala to teach "that cells may be frozen when they are encapsulated in a hydrogel matrix" and "would not predict that Usala's materials would be useful when cells are not encapsulated and would not predict that cryopreservation temperatures as presently recited may be utilized when cells are not encapsulated." *Id.*

Appellants also argue claims 4–6 are not obvious because "Frondoza is silent as to any aspect of cryopreservation" and "Usala does not cure this deficiency because Usala only teaches cryopreservation of encapsulated cells and not cells that are attached to particles." Br. 16–17.

These arguments are unpersuasive because the Examiner's rejection is based on the combined teachings of Frondoza and Usala. *See* Ans. 12–16. We agree with the Examiner that nonobviousness cannot be established by attacking the references individually when the rejection is predicated upon a combination of prior art disclosures. *In re Merck & Co. Inc.,* 800 F.2d 1091, 1097 (Fed. Cir. 1986); *see also In re Keller,* 642 F.2d 413, 426 (CCPA 1981) (finding "one cannot show nonobviousness by attacking references individually where, as here, the rejections are based on combinations of references" (citations omitted)). Thus, whether Frondoza or Usala individually fails to teach a cell-seeded composition wherein particles of a cross-linked hydrogel matrix with cells attached thereto are in combination with a cryoprotectant is not dispositive to the sufficiency of the rationale underlying the rejection. As stated by the Examiner, Frondoza teaches compositions for cell-microcarriers, including hydrogels that comprise multiple components as disclosed by the Specification and that can be cryopreserved. FF6 and 8. The Examiner has also established that Usala discloses a method of maintaining cell viability and functioning during storage where a matrix protects cells during frozen storage and that storage temperatures can be -20°C. FF13. The disclosed method includes addition of a cryoprotectant to the matrix. FF15. The Examiner sufficiently establishes that an ordinary artisan reading Frondoza and Usala in

combination would have reasonably expected that the methods for cryopreservation and the cryoprotectants disclosed in Usala would likewise useful in cryopreserving the cell-microcarriers of Frondoza. Ans. 12–16.

Appellants next argue that dependent claims 8–13, 17, 18, and 32–35 are not obvious because "the examiner has not shown how a person of skill in the art may arrive at a composition based upon the disclosure of Frondoza that would inherently exhibit the properties recited." Br. 17. This argument is not persuasive.

We have addressed the obviousness of the teachings of Frondoza and Usala above. With regard to Appellants' argument that the Examiner did not establish that the elements of the dependent claims were inherent,

> "'it is elementary that the mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not cause a claim drawn to those things to distinguish over the prior art. Additionally, where the Patent Office has reason to believe that a functional limitation asserted to be critical for establishing novelty in the claimed subject matter may, in fact, be an inherent characteristic of the prior art, it possesses the authority to require the applicant to prove that the subject matter shown to be in the prior art does not possess the characteristic relied on.'" *In re Best*, 562 F.2d 1252, 1254–55, (CCPA 1977) (quoting *In re Swinehart*, 439 F.2d 210, 212–13 (CCPA 1971)).

The Examiner finds that "the microcarrier particle [that can be produced from the Frondoza teachings such as] (cross-linked gelatin-dextran hydrogel; the scaffold – microcarrier particles can be porous)" would inherently possess the properties recited claims 8–13, 17, 18, and 32–35. Ans. 8. Appellants have presented no evidence to prove that the elements of the

dependent claims are not present. Without evidence, Appellants' attorney argument fails to rebut the prima face case.

Appellants next argue that claims 8–13 and 32–35 are not obvious because the Examiner has "pointed to nothing in Frondoza teaching the use of porous particles . . . The only porous materials discussed in Frondoza are porous scaffolds that may have the pores filled to form a tissue-like matrix. This, however, does not teach porous particles of a hydrogel matrix and certainly does not teach particles having specifically defined porosities." Br. 18. Similarly, Appellants argue claims 17–18 are not obvious because "the examiner has pointed to nothing in Frondoza teaching attachment of a defined number of cells to a particle." *Id.* These arguments are not persuasive.

As discussed above, Appellants claim a generic cross-linked bioactive hydrogel matrix. Frondoza discloses the use of hydrogels as cell-microcarriers as well as the use of a "porous biodegradable scaffold." FF8 and 12. Absent evidence to the contrary, we agree with the Examiner that it is obvious to combine these two components, "each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. . . . [T]he idea of combining them flows logically from their having been individually taught in the prior art." *In re Kerkhoven,* 626 at 846, 850 (CCPA 1980). We further agree with the Examiner that "[a] person of ordinary skill in the art would adjust the pores, the porosity or the particle size of the scaffold based on tissue characteristics needed for cell growth." The Supreme Court has found "[a] person of ordinary skill in the art is also a person of ordinary

creativity, not an automaton." *KSR International* Co. *v. Teleflex Inc.,* 82 USPQ2d at 1397. Appellants have provided insufficient evidence that the claimed number of cells is impossible to reach within the disclosures of Frondoza. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 456 (CCPA 1955). Absent evidence to the contrary, the disclosures in Frondoza are sufficient to render obvious the elements of claims 8–13, 17, 18, and 32–35.

Appellants next argue that "cross-linked hydrogels can provide properties that would not be expected based on knowledge of the properties of the separate materials alone." Br. 19. Appellants argue Figure 4, reproduced below, shows that

> in relation to a hydrogel formed from cross-linking gelatin with dextran . . . fibroblast cells exhibit only about 40% aggregation when left untreated. When fibroblasts were treated with collagen monomer alone or dextran alone . . . only about 20 to 25% of the cells were aggregated . . . when treated with the hydrogel formed from dextran and gelatin, at least 80% of the cells present were in an aggregated state.

Br. 19.

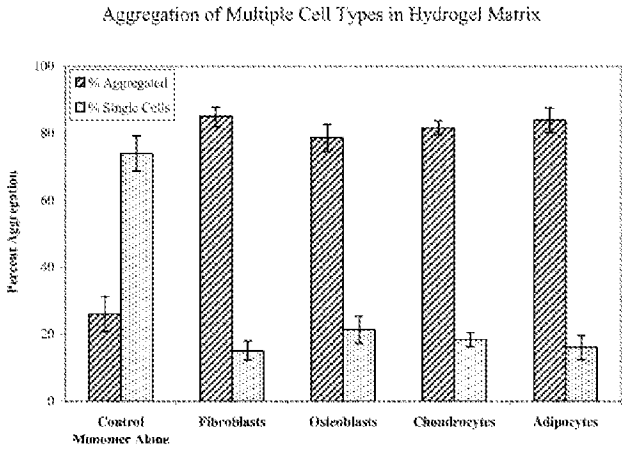

FIG. 4

Figure 4 depicts a bar chart showing the percent of aggregation of multiple cell types in a hydrogel matrix.

Appellants claim the skilled artisan "with knowledge of Frondoza would not expect that the use of a polymer alone would reduce cell aggregation while a hydrogel formed from a combination thereof would dramatically increase cell aggregation." *Id.* at 19–20.

We are not persuaded. Appellants have not presented persuasive evidence that the use of their cross-linked hydrogels is not obvious. "[B]y definition, any superior property must be *unexpected* to be considered evidence of non-obviousness." *Pfizer, Inc.* v. *Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). Appellants' arguments point to data in Figure 4 of the Specification, but this data is not sufficient for our analysis. Data for a single "control monomer" is shown, but without identification of the cell type, which may not match the tested cell types. In addition, this data does not compare against the hydrogel taught by Frondoza, the closest prior art. "To be particularly probative, evidence of unexpected results must establish

that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). We find no error in the Examiner's understanding of claims 8–13, 17, 18, and 32–35 or analysis of the prior art.

Appellants next argue that claims 14–16 and 36 are not obvious because "[n]othing in Qian suggests that the hemostatic sealants discussed therein would be suitable as cell-seeded microcarriers . . . The examiner [has] not shown that a person of skill in the art would predict that a ground hydrogel as taught by Qian would be a suitable cell-seeded microcarrier." Br. 20.

We are not persuaded. The Specification teaches "[t]he bioactive hydrogel matrix can be in particulate form when combined with the cells for cryopreservation." FF4. Qian teaches a dry cross-linked gelatin powder that can be cross-linked, dehydrated, and ground. FF16–17. The particle sizes disclosed range from 150 μm to 750 μm, and Qian suggests "particle sizes outside of this preferred range may find use in many circumstances." FF18. Given this teaching and the express suggestion to use other particle sizes as desired, we agree with the Examiner that the invention disclosed by claims 14–16 and 36 is obvious, absent any evidence to the contrary from Appellants.

Similarly, with regard to claim 29, Appellants argue "the examiner has pointed to nothing in Hill that cures the various failures of Frondoza discussed above . . . a person of skill in the art viewing Frondoza would have

no reason to attempt to modify the disclosure of Frondoza utilizing teaching from Hill." Br. 20. Appellants further argue the Examiner did not make a showing that the combination is predictable. *Id.* at 21.

These arguments are not persuasive because they are merely attorney argument without evidence. Hill teaches that a hydrogel may be dehydrated by "[a]ny method known in the art," including freeze drying, and then ground to particulate form. FF19–20. We agree with the Examiner that Appellants' claim 29 is obvious in light of Hill and Frondoza, and that the Examiner has established that the skilled artisan would have a reasonable predictability of success making the invention of claim 29. *In re O'Farrell*, 853 F.2d at 903–04. We find no error in the Examiner's rejection of claim 29.

Conclusion of Law

In summary, we find a preponderance of the evidence supports the Examiner's conclusion that claims 1–6, 8–19, 21–25, 27–30, 32–41, 43, and 44 are obvious over the cited art.

SUMMARY

We affirm the rejection of claims 1, 2, 8–13, 17–19, 21–25, 27, 28, 30, 32–35, and 37–41 under 35 U.S.C. § 103(a) as obvious over Frondoza.

We affirm the rejection of claims 14–16 and 36 under 35 U.S.C. § 103(a) as obvious over Frondoza and Qian.

We affirm the rejection of claim 29 under 35 U.S.C. § 103(a) as obvious over Frondoza and Hill.

We affirm the rejection of claims 3–6, 43, and 44 under 35 U.S.C. § 103(a) as obvious over Frondoza and Usala.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED